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MERCURIAL DIURETICS

The oral thiazides have largely replaced the mercurial diuretics, but the parenteral mercurials are still valuable agents, especially for patients who are sensitive to the thiazides or who cannot take oral medication. The oral and rectal mercurials are much inferior to either the thiazides or the parenteral mercurials; and rectal administration sometimes causes proctitis. The leading parenteral preparations are meralluride (Mercuhydrin - Lakeside), mercaptomerin (Thiomerin - Wyeth), and mersalyl (Salyrgan-Theophylline - Winthrop). To improve absorption and reduce toxicity and local irritation, Mercuhydrin and Salyrgan contain theophylline and Thiomerin contains a sulfhydryl group.

PARENTERAL ROUTES - Intramuscular administration gives optimal diuretic effect with a minimum of local and systemic reactions (when the buttocks or the thighs are edematous, the deltoids should be used). Rapid intravenous administration occasionally causes sudden death, probably from cardiac arrhythmias in previously damaged hearts; slow injection greatly reduces this risk. With intramuscular injection, diuresis begins in about an hour or two, reaches a peak in six to nine hours, and ceases after 12 to 24 hours. As with other diuretics, many variables affect the response to mercurials. Extreme reduction of glomerular filtration by renal or cardiac disease, for example, may prevent significant diuresis. Excessive aldosterone secretion in patients with liver cirrhosis or nephrosis may have the same effect; for such patients, spironolactone (Aldactone - Searle) may be added (see The Medical Letter, 2:49, 1960).

SIDE EFFECTS - Fever, rashes, urticaria, exfoliative dermatitis, and other sensitivity reactions are much less frequent than with the thiazides. Any potent diuretic, including the mercurials, may cause sodium deficiency, with such symptoms as drowsiness, confusion, headache, thirst, faintness and leg cramps; hyponatremia is particularly likely after prolonged and frequent administration to a seriously sick patient on restricted salt intake. Hypokalemia is less of a problem than with the thiazides, but potassium supplements are occasionally needed. Patients receiving intensive mercurial therapy should be watched carefully for electrolyte disturbances, including hypochloremic alkalosis. Like the thiazides, mercurial diuretics occasionally precipitate attacks of gout.

Mercurials are unlikely to be effective when a thiazide in optimal dosage has failed (and vice versa), and it is doubtful that they have greater diuretic ef-

fect. A recent well-controlled study (H. Gold, et al., JAMA, 173:745, 1960) indicates that 2 cc. of meralluride intramuscularly produces a greater weight loss at the end of 24 hours than a single daily dose of 2 Gm. of chlorothiazide. But the diuretic effect of chlorothiazide is markedly enhanced when it is taken in divided doses (W. G. Walker, et al., J. Chronic Dis., 10:47, 1959).

DOSAGE - One to 2 cc. of Mercuhydrin, Thiomerin or Salyrgan is administered daily for a period of several days, if necessary; the frequency of dosage is adjusted thereafter on the basis of weight changes and other evidence of change in body fluid. Diamox or another carbonic anhydrase inhibitor, either alone or in conjunction with ammonium chloride, may restore or potentiate response to mercurials, but the last dose must be taken six hours or more before the mercurial is administered.

Ammonium chloride in doses amounting to 3 to 9 Gm. daily for two or three days is often used to enhance the effect of mercurial diuretics or to restore responsiveness to them. Since absorption from enteric-coated capsules is uncertain, the ammonium chloride is best administered as a syrup. Ammonium chloride should not be used if significant acidosis is present, either respiratory or metabolic, or if liver function is significantly reduced. Calcium chloride (4 to 12 Gm. daily) is as effective as ammonium chloride and has the advantage in patients with cirrhosis of not increasing the blood ammonia. Because calcium chloride is hygroscopic it should also be given as a syrup. In some patients gastric intolerance limits the usefulness of either of these salts. For such patients, l-lysine monohydrochloride, 10 Gm. four times daily in fruit juice (A. L. Rubin, et al., Circulation, 21:332, 1960), or intravenous infusions of l-arginine monohydrochloride (L. I. Gidekel, et al., N.E. J. Med., 263:221, 1960) may be tried.

BELLERGAL

Bellergal (Sandoz) exemplifies many of the weaknesses of fixed-ratio drug combinations. Bellergal tablets contain 0.1 mg. Bellafoline, 0.3 mg. ergotamine tartrate and 20 mg. phenobarbital; they are promoted for the prevention of migraine headaches, and for the relief of menopausal, menstrual and gynecologic symptoms, gastrointestinal disorders, "cardiac neuroses," and anxiety.

The effects of Bellafoline and ergotamine tartrate last for only about four hours; phenobarbital is slowly metabolized and excreted, so that residual effects continue for as much as 24 to 72 hours. Dosage every four to six hours leads to cumulative action of the phenobarbital, and the major effect of the combination is likely to be sedation. Similar effects are seen with many other fixed-ratio combinations of anticholinergic drugs and phenobarbital.

ADDED DRUGS INEFFECTIVE - For most patients, moreover, the addition of a second or a third drug to the needed drug in such a fixed combination serves no useful purpose and only increases the likelihood of unwanted side effects. Thus, in gastrointestinal disorders such as peptic ulcer and irritable colon, there is no evidence that ergotamine tartrate adds to the effectiveness of Bellafoline in relieving either spasm or excessive gastric secretion. Furthermore, the small

amount of Bellafoline in a dose of Bellergal is likely to be inadequate when atropine-like effects are desired.

There is no agreement among authorities that any drug can be relied on to prevent migraine, but the drug most likely to be effective is ergotamine tartrate in adequate doses by mouth, inhalation, injection, or rectal instillation. It has not been shown that Bellafoline adds to the effectiveness of ergotamine tartrate in preventing attacks of migraine. (See The Medical Letter, 2:54, 1960 for discussion of hazards and cautions in the use of ergotamine tartrate.) For anxiety, and for menopausal, menstrual and gynecologic disorders, various single drugs often provide relief of symptoms, and in none of these conditions is the combination of agents present in Bellergal indicated.

GAMMA GLOBULIN

Immune gamma globulin is the only available agent affording protection against several viral diseases, and its use following exposure often prevents or attenuates the disease. It also provides effective prophylaxis against recurrent bacterial infections in agammaglobulinemia (or hypogammaglobulinemia). Its value in many diseases in which it is sometimes used is, however, questionable. At best, gamma globulin gives only transitory protection and is not a substitute for effective vaccines.

Most antiviral, antibacterial, and antitoxic antibodies are gamma globulins; commercial preparations containing the required globulins (165 mg. per cc.), and effective against one or more organisms or toxins, are obtained from pooled plasma or minced placenta of healthy donors. (Color differences among gamma globulin preparations result from differences in source.)

HYPO- OR AGAMMAGLOBULINEMIA - In this congenital or acquired defect in antibody response, recurrent infection by pyogenic organisms can be prevented by raising the concentration of circulating gamma globulin to 150 mg. per hundred cc. This level can be achieved with initial dose of 0.6 cc. per pound of body weight and maintenance doses of 0.3 cc. per pound administered intramuscularly at monthly intervals to children and semimonthly to adults (circulating gamma globulin disappears more rapidly in adults). The frequency of administration must at times be changed on the basis of clinical response.

MEASLES - During the first six days after exposure, a dose of 0.1 cc. per pound is given for prevention of measles in children under the age of two years. The attenuation dose under two years is 0.02 cc. per pound, and for older children, 0.04 cc. per pound. There is suggestive evidence that attenuation lowers the incidence of encephalitis; and many physicians believe that attenuation — with an attack usually conferring permanent immunity — is preferable to prevention regardless of the age of the patient.

RUBELLA - Twenty cc. of gamma globulin has been used for prevention of rubella after exposure during the first three months of pregnancy, but its effectiveness is questionable.

INFECTIOUS HEPATITIS - Most Medical Letter consultants recommend 0.01 to 0.02 cc. per pound administered as promptly as possible after exposure; a few authorities believe that doses as high as 0.05 or 0.06 cc. per pound should be used for greater certainty (S. Krugman, et al., JAMA, 174: 823, 1960).

POLIOMYELITIS - Although gamma globulin is considered protective, by the time a case is recognized it is too late for effective use. The American Academy of Pediatrics does not recommend its use for this purpose.

VACCINIA - Eczema and agammaglobulinemia are major contraindications to small-pox vaccination. For the prevention of disseminated vaccinia in unprotected persons exposed to recently vaccinated contacts and for treatment of eczema vaccinatum and generalized vaccinia, Vaccinia Immune Globulin (V.I.G.) is effective and can be obtained through special regional consultants of the Red Cross.

MUMPS - Although hyperimmune gamma globulin has been recommended for prophylaxis of exposed male adults who have no previous history of mumps and whose skin tests are negative, and to prevent orchitis complications, the consensus of Medical Letter consultants is that at best the globulin is only occasionally effective for either indication.

PERTUSSIS - For the prevention of pertussis in exposed infants, in whom mortality is high, 2.5 cc. of hyperimmune gamma globulin should be given promptly, and repeated once after 5 days. For treatment, 2.5 cc. may be given every other day for three to five doses, though effectiveness is questionable.

OTHER USES - The enthusiastic clinical reports on its use in the prevention and treatment of respiratory and other infections are based largely on uncontrolled and unreliable observations. Improvement after the administration of gamma globulin has been reported in children with persistent or recurrent upper respiratory viral infections. A controlled study (K. C. Finkel, et al., Pediatrics, 25: 798, 1960), however, showed no difference in recovery time in patients with comparable infections with or without 0.2 cc. per pound of gamma globulin. Similar studies of cross infections in nursery population have shown no significant difference between gamma-globulin-treated and control infants.

The need for controls was made clear in a double-blind study of gamma-globulin therapy in asthmatic children with infections (R. S. Abernathy, et al., Pediatrics, 21: 980, 1958); the authors found gamma globulin to have no prophylactic or therapeutic value. Recurrent boils have been treated with gamma globulin but controlled experiments have not been reported.

SIDE EFFECTS - Because intravenous administration may cause severe cardiac arrhythmias, hypotension and hyperpyrexia, gamma globulin should be administered intramuscularly. Large intramuscular doses may cause local inflammation with malaise, headache and low-grade fever. Rare instances of angioneurotic edema, nephrotic syndrome and anaphylactic shock have been reported.

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